1600 #12
PATENT APPLICATION
Docket No.: 2727.1001.30002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant:	Eileen Louise Rice McFarland		
Application No.:	09/724,135	Group Art Unit:	1641
Filed:	November 28, 2000	Examiner:	K. Padmanabhan
For:	METHOD FOR DIAGNOSING A PREDISPOSITION OF PSYCHOSIS IN A PROGENY		

CERTIFICATE OF MAILING

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on 09/04/02 Stephanie L Carta
Date Signature

Stephanie L. Carta
Typed or printed name of person signing certificate

BRIEF ON APPEAL

Box AF
Assistant Commissioner for Patents
P.O. Box 2327
Arlington, VA 22202

Sir:

This Brief on Appeal is submitted pursuant to the Notice of Appeal received in the U.S. Patent and Trademark Office on June 4, 2002, and in support of the appeal from the final rejection set forth in the Office Action mailed on March 26, 2002. The fee for filing a brief in support of an appeal is enclosed. A Petition for Extension of Time and the appropriate fee are being filed concurrently.

I. PARTY IN INTEREST

The party in interest is Eileen Louise Rice McFarland, 15 Cefalo Road, West Roxbury, Massachusetts, 02132.

II. RELATED APPEALS AND INTERFERENCES

Appellant and the undersigned Attorney are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1-13 have been finally rejected and a copy of pending claims, as they stood upon final rejection, appears in Appendix A of this Brief. Claims 1, 5-8, and 10-12 were amended in the Amendment filed on February 11, 2002. Claim 10 was amended and Claims 12 and 13 were added in the Amendment filed July 25, 2001. Claims 2-4 and 9 appear as originally filed. Claims 1, 5, 6 and 11 are amended in the Amendment After Final Rejection, filed concurrently with this Brief. The claims have been amended to address minor informalities. The pending claims, as amended by the Amendment After Final Rejection, appear in Appendix B of this Brief.

IV. STATUS OF AMENDMENTS

Two papers have been filed subsequent to the Final Rejection. The first paper was a Notice of Appeal received in the U.S. Patent and Trademark Office on June 4, 2002. The second paper is an Amendment After Final Rejection Under 37 C.F.R. §1.116, delivered under Certificate of Mailing concurrent with this Appeal. The second Response amended Claims 1, 5 and 11. A copy of the Claims as finally amended appears in Appendix B of this Brief.

V. SUMMARY OF INVENTION

The claimed invention pertains to a method for aiding in a diagnosis of a predisposition to psychosis in a progeny who possesses Cw blood antigen, comprising obtaining a biological sample from the mother of the progeny and determining the presence of anti-Cw antibody in the biological sample, where the presence of an anti-Cw antibody in the biological sample is indicative of a predisposition of the progeny to psychosis. (Claims 1-5, 11 and 13).

In another embodiment, the invention relates to a method of screening for a predisposition to psychosis, comprising obtaining a biological sample from a maternal donor and determining the presence of anti-Cw antibody in the sample, wherein the presence of an anti-Cw antibody is indicative of a predisposition to psychosis in the progeny if the donor's progeny possess Cw antigen. (Claims 6-9).

The invention further relates to a kit for use in diagnosis of psychosis comprising a sample of anti-Cw antibody and detector that binds to anti-Cw antibody. (Claims 10 and 12).

The methods of the present invention provide simple detection of the presence of an antibody to a rare blood factor that is indicative of a predisposition to psychosis. Additionally, these methods do not rely solely on a clinical diagnosis.

VI. ISSUES

The following issues are on appeal:

A. Whether Claims 1-13 are properly rejected under 35 U.S.C. § 112, first paragraph, as not disclosing in the specification sufficient information to allow one skilled in the art to make and use the invention, commensurate with the full scope of the claims, without undue experimentation. Specifically, the Examiner questions the sufficiency of the case study.

B. Whether Claims 1-5 and 11 are properly rejected under 35 U.S.C. § 112, second paragraph, as not providing sufficient antecedent basis for specific limitations in the claims and therefore not distinctly claiming the subject matter the applicant regards as the invention.

VII. GROUPING OF CLAIMS

Claims 1-5 stand or fall together. Specifically, Claims 1-5 relate to a method of aiding in a diagnosis of a predisposition to psychosis in a progeny who possesses Cw blood antigen, comprising obtaining a biological sample from the mother of the progeny and determining the presence of anti-Cw antibody in the biological sample, where the presence of an anti-Cw antibody in the biological sample is indicative of a predisposition of the progeny to psychosis.

Claims 6-9 stand or fall together. Specifically, Claims 6-9 relate to a method of screening for a predisposition to psychosis, comprising obtaining a biological sample from a maternal donor and determining the presence of anti-Cw antibody in the sample, wherein the presence of

an anti-Cw antibody is indicative of a predisposition to schizophrenia in the progeny if the donor's progeny possess Cw antigen.

Claims 10 and 12 do not stand or fall with the other claims because Claims 10 and 12 contain additional limitations which further distinguish the subject matter of Claims 10 and 12 from the other claims. Specifically, Claims 10 and 12 relate to a **product**, a kit comprising anti-Cw antibody, a detector that binds to anti-Cw antibody and instructions for use, used to aid in diagnosing a predisposition to psychosis. Whereas, Claims 1-9, 11 and 13 relate to **methods** of aiding in a diagnosis or screening for a predisposition to psychosis utilizing anti-Cw antibody.

VIII. ARGUMENT

A. Whether Claims 1-13 are properly rejected under 35 U.S.C. § 112, first paragraph, as not disclosing in the specification sufficient information to allow one skilled in the art to make and use the invention, commensurate with the full scope of the claims, without undue experimentation. In particular, whether Appellant has enabled the invention and provided significant and evidence working examples.

i. Summary of Examiner's Rejection

Claims 1-13 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner presented four arguments in support of this assertion. (Office Action mailed March 26 ,2002, pages 2-3, ¶ 2). First, "many dispositions, outside the realm of psychotic disorders may be determined by measuring [Cw] antibodies." Second, "Cw is relatively rare and no previous definitive correlation has been demonstrated between the measurement of [Cw] antibodies and psychosis." Third, "there is insufficient guidance and working examples in the specification to enable one of skill in the art to determine predisposition to psychosis by measuring anti-[Cw] antibodies." Fourth, "the disclosure of applicant has not enabled the determination of predisposition to all types of psychosis."

ii. Arguments in Support of Patentability

Appellant has disclosed a method for use in aiding in a diagnosis of a predisposition to psychosis where the presence of an anti-Cw antibody in a progeny with Cw antigen can be

indicative of a predisposition to psychosis in that progeny. Predisposition means a tendency to a condition that is usually based on the combined effects of genetic and environmental factors. Predisposition confers an increased susceptibility to psychosis. As disclosed in the Application, a link has been established through the case study presented and other medical evidence such that a propensity for mental illness from pregnancy complications can be used in aiding in a diagnosis of a predisposition to psychosis, in particular schizophrenia. The actual diagnosis of psychosis must be made through clinical diagnosis. However, the presence of anti-Cw antibodies can be used as a tool for aiding in a diagnosis of a predisposition, so that early intervention may be established, thus resulting in a better prognosis. A clinical diagnosis of psychosis, schizophrenia being an example, is a subjective undertaking based on the variables presented to the clinician at the time of treatment and the current understanding and definition of the disease. Because the medical establishment frequently updates its understanding of these complex disorders and modifies the clinical variables required for a specific diagnosis, the presence of Cw antigen can be used to aid in a diagnosis of a broad range of psychoses. Appellant has demonstrated that a problem with histocompatibility, shown by the presence of an anti-Cw antibody, is a tool to **aid** in the diagnosis of psychosis.

The Examiner first asserts that many dispositions, outside the realm of psychotic disorders, may be determined by measuring Cw antibodies. Appellant directs the Board to Mouro *et al.*, (*Blood*, 86(3):1196-1201 (1995) (Exhibit A) which describes the molecular basis of the Rh blood group antigens, particularly that sequence analysis has indicated the expression of Cw antigens is associated with point mutation in the RHCE gene and further describes a polymerase chain reaction assay useful to diagnose the Cw status of fetuses for the proper management of pregnancies in highly Cw immunized mothers. (hemagglutination inhibition experiments utilizing anti-Cw antibodies). Curtin *et al.* (*Am. J. of Med. Tech.*, 33:175-178 (1967)) (Exhibit B) and Bowman *et al.* (*Vox Sanguinis*, 64:226-230 (1993)) (Exhibit C) both describe hemolytic disease due to anti-Cw antibody. These references, while not teaching or suggesting Appellant's discovery of a link between the presence of the anti-Cw antibody and a predisposition to psychosis, do provide evidentiary support for some of the adverse effects of histocompatibility. The presence of the anti-Cw antibody in a progeny with Cw antigen is indicative of a histocompatibility, of which hemolytic disease is a severe example. Contrary to

the Examiner's contention, these disorders are not unrelated. A profound relationship exists between histocompatibility and hemolytic disease. Further, a link has been established between pregnancy complications and mental illness. Additionally, Appellant teaches a method to aid in diagnosing a predisposition to psychosis and does not require the method to equivocally differentiate between psychosis and hemolytic disease.

Appellant directs the Board to evidence, supported by the case study and the prior art, indicating that histocompatibility of the Cw antigen can be a risk factor in schizophrenia. For example, a link between HLA histocompatibility and psychosis, in particular schizophrenia, has been established (Wright, P. *et al.*, *Schizophrenia Research*, 47(1):1-12 (2001)), Abstract, Exhibit D). Although the evidence provided is not conclusive, this reference indicates a susceptibility may exist. Accordingly, it should be considered by the Examiner.

The Examiner further asserts that since Cw is relatively rare and no previous correlation has been demonstrated between the measurement of Cw antibodies and psychosis, a method attempting to link the two inherently encompasses a great amount of uncertainty, which the current state of the art is unable to remedy. Appellant respectfully disagrees with the Examiner's conclusion. The art is filled with relevant and related studies showing that the link between the presence of auto antibodies and mental illness is not uncertain, as is detailed below.

The incidence of Cw antigen is rare, and coincidentally the same as schizophrenia; approximately 1% of the population is affected. Ivanyi *et al.* found a highly significant increase in Cw4 antigen among schizophrenics, which was neither connected with the age of the patients at the onset of disease nor with the age at the time of testing and the duration of the disease (*Tissue Antigens*, 9:41-44 (1977)), (Exhibit E). While this reference does not each Appellant's method of aiding a diagnosis of schizophrenia, it does establish the link between the presence of Cw antigen and schizophrenia. Interestingly, Finland has both an increased incidence of schizophrenia and Cw antigen. Also, certain ethnic populations have been implicated as being predisposed to a higher incidence of schizophrenia. Chowdari *et al.* describe immune related genetic polymorphisms, particularly in the HLA region, and schizophrenia among the Chinese (*Human Immunology*, 62:714-724 (2001)), (Exhibit F). The state of the art is filled with relevant and related studies, such as HLA linkage, histoincompatibility, pregnancy complications and the case study presented herewith, that show this link is not uncertain.

The Examiner also argued the insufficiency of the case study. Appellant respectfully disagrees. The case study, in combination with the state of the art, sufficiently links the Cw antigen antibody to teach the method used in aiding the diagnosis of one with psychosis, in particular, schizophrenia. Additionally, working examples are not required to be provided in support of the claims. *See In re Robbins*, 166 U.S.P.Q. 552 (C.C.P.A. 1970) (Exhibit G). The state of the art has established a link between the HLA region and schizophrenia and psychosis through linkage studies on chromosome 6. The Hollister *et al.* study concluded that Rh incompatibility contributes to schizophrenia (*Arch. Gen. Psychiatry*, 53(1): 19-24 (1996)) (Exhibit H). The locus of Cw is found on chromosome 6 in the HLA region. Lindholm *et al.* report a schizophrenia-susceptibility locus at 6q25 in one of the world's largest reported pedigrees (a 12 generation, 3,400 member family) (*Am. J. Hum. Genet.*, 69(1):96-105 (2001), Exhibit I). Although the particular genes have not yet been identified, there is growing evidence that the areas of concern link the same area that encodes the blood group antigens, *i.e.*, the same area that encodes the blood antigen, Cw. Also, these studies may indicate the presence of small effector genes that relate to a subset of the schizophrenic population. For example, Bassett and Chow disclose that a 22q11 deletion syndrome is a genetic subtype of schizophrenia (*Biol. Psychiatry*, 46:882-891 (1999)), (Exhibit J). Lahdelma *et al.* disclose an association between HLA-A1 allele and schizophrenia gene(s) in patients refractory to conventional neuroleptics but responsive to clozapine medication (*Tissue Antigens*, 51:200-203 (1998)), (Exhibit K). The state of the art provides sufficient evidence of a relationship between the HLA region and schizophrenia predisposition to support Appellant's further contention that patients found to be exposed specifically to anti-Cw antibody can anticipate an increased incidence of schizophrenia diagnosis.

Schizophrenia is a genetically complex disorder in which both genetic and environmental factors may contribute. Appellant has provided evidence to be used in **aiding** in a diagnosis of a predisposition to psychosis, particularly schizophrenia. Appellant provides evidence that the presence of the anti-Cw antibody can be indicative of a predisposition to psychosis and this evidence may be used in aiding the diagnosis to psychosis. Appellant is not claiming that the presence of the anti-Cw antibody is equivocally indicative of psychosis. However, detection of Cw antibody, when used in combination with clinical diagnostic methods, can be used to

proactively determine if a person is predisposed to psychosis. Appellant has determined that the presence of the anti-Cw antibody is a risk factor which can be screened for in a psychosis assessment. The Examiner's assertion that Appellant's use of the word "can" inherently indicates that the method may not work is erroneous. Appellant is not suggesting such an inference. As stated, the presence of the antibody has been shown to be a risk factor and can be indicative of a predisposition.

Environmental factors also contribute to psychosis, in particular schizophrenia. For example, Basset and Chow discuss risk factors and propose clinical criteria to aid in identifying patients with schizophrenia who have a genetically identifiably subtype of schizophrenia (*Biological Psychiatry*, 46(7):882-891 (1999)) (Exhibit J). Appellant's discovery of another risk factor (*i.e.*, presence of anti-Cw antibody) may contribute to better or earlier diagnosis.

Appellant respectfully disagrees with the Examiner's assertion that Appellant has not enabled the invention. Appellant's invention relates to a method for aiding in a diagnosis of a predisposition to psychosis. A showing of enablement requires only that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. *See In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). Appellant need not provide a working example for all types of psychosis but only provide a reasonable correlation to the scope of the claims. Appellant has done so in the case study example. Satisfaction of the enablement requirement of §112 is not precluded by the necessity for some experimentation, as long as undue experimentation is not required. *See In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). In fact, a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *See In re Jackson*, 217 U.S.P.Q. 804 (Bd. App. 1982). The experimentation required by the invention for aiding in a diagnosis of a predisposition to psychosis is simply obtaining a biological sample and determining the presence of an antibody. The experimentation required to accomplish this task is certainly not undue, and can be routinely performed by one of skill in the art. When the invention and the evidence are considered as a whole, Appellant has provided the necessary enablement to make and use the invention as claimed.

In view of the above remarks and comments, Appellant respectfully requests reconsideration and withdrawal of the rejection.

B. Whether Claims 1-5 and 11 are properly rejected under 35 U.S.C. § 112, second paragraph, as not providing sufficient antecedent basis for specific limitations in the claims and therefore not distinctly claiming the subject matter the applicant regards as the invention.

Claim 1 was rejected as not providing sufficient antecedent basis for the language "the diagnosis" and "the progeny's mother." (Office Action mailed March 26, 2002, page 3, ¶ 5).

Claim 1 has been amended to read "A method for aiding in a diagnosis...." Support for this language may be found in the Specification at page 6, lines 17-26.

Appellant contends that "the progeny's mother" does not lack sufficient antecedent basis. The Examiner is directed to preliminary language in Claim 1 defining "the progeny" as "...a progeny who possesses Cw blood antigen." Appellant contends this description particularly points out the relationship between the specific progeny at issue and the mother of such a progeny, and disagrees with the Examiner that there may be a more clear manner in which to represent this relationship.

It is respectfully requested that Independent Claim 1 and Dependent Claims 2-5, 12 and 13 be allowed to pass to issue as distinctly claiming the subject matter which is the invention.

Claim 5 was also rejected as not providing sufficient antecedent basis for the language "the same." (Office Action mailed March 26, 2002, page 4, ¶ 6).

Claim 5 has been amended to read "...wherein the mother and progeny have a compatible blood type." Support for this language may be found in the Specification at page 5, lines 1 through 9 and page 7, line 21. It is respectfully requested that Claim 5 be allowed to pass to issue as distinctly claiming the subject matter which is the invention.

Claim 11 was also rejected as not providing sufficient antecedent basis for the language "the diagnosis." (Office Action mailed March 26, 2002, page 4, ¶ 7).

Claim 11 has been amended to read "A method for diagnosing or aiding in a diagnosis...." Support for this language may be found in the Specification at page 6, lines 17 through 26. It is

respectfully requested that Claim 11 be allowed to pass to issue as distinctly claiming the subject matter which is the invention.

CONCLUSION

In view of the foregoing arguments, it is respectfully requested that the rejections be reversed and that the claims be allowed. This Brief is being filed in triplicate.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

Alice O. Carroll
Registration No.: 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Date: September 4, 2002

APPENDIX A: Claims as Pending Upon Final Rejection.

What is claimed is:

1. (Amended) A method for aiding in the diagnosis of a predisposition to psychosis in a progeny who possesses Cw blood antigen, comprising:

(a) obtaining a biological sample from the progeny's mother; and

(b) determining presence of anti Cw antibody in the biological sample,

wherein the presence of an anti Cw antibody in the biological sample is indicative of a histocompatibility and a predisposition of the progeny to psychosis.

2. A method as in claim 1 wherein the psychosis is schizophrenia.

3. A method as in claim 1 wherein the psychosis is an axis I disorder.

4. A method as in claim 1 wherein the psychosis is an axis II disorder.

5. (Amended) A method as in claim 1 wherein the mother and progeny have a blood type which is the same.

6. (Amended) A method of screening for predisposition to psychosis, comprising:

(a) obtaining a sample from a maternal donor; and

(b) determining presence of an anti-Cw antibody in the sample,

wherein the presence of an anti-Cw antibody is indicative of a predisposition to schizophrenia if donor's progeny possess Cw antigen.

7. (Amended) A method as in Claim 6 wherein the progeny has a family history of psychosis.

8. (Amended) A method as in Claim 6 wherein the donor is pregnant.

9. A method as in Claim 8 wherein the donor is post-partum.

10. (Twice Amended) A kit for use in diagnosis of psychosis, comprising a sample containing anti-Cw, a detector that binds to anti-Cw antibody, and instructions for using the antibody and detector to diagnose a predisposition to psychosis.

11. (Amended) A method for diagnosing or aiding in the diagnosis of a predisposition to a psychotic disorder, comprising determining presence of anti-Cw antibody in a sample from an individual with Cw antigen, wherein the presence of anti-Cw antibody indicates a positive diagnosis.

12. (Amended) A kit for use in diagnosis of psychosis, comprising a sample containing anti-Cw antibody, a detector that binds to anti-Cw antibody; and instructions for utilization of the kit according to the method of Claim 1.

13. (New) The method of Claim 1, further comprising utilizing a kit, comprising a sample of anti-Cw antibody, a detector that binds to anti-Cw antibody; and instructions for using the antibody and detector to diagnose a predisposition to psychosis.

APPENDIX B: Claims as Amended After Final Rejection.

What is claimed is:

1. (Twice Amended) A method for aiding in [the] a diagnosis of a predisposition to psychosis in a progeny who possesses Cw blood antigen, comprising:

(a) obtaining a biological sample from the progeny's mother; and

(b) determining presence of anti Cw antibody in the biological sample,

wherein the presence of an anti Cw antibody in the biological sample is indicative of a histocompatibility and a predisposition of the progeny to psychosis.

2. A method as in claim 1 wherein the psychosis is schizophrenia.

3. A method as in claim 1 wherein the psychosis is an axis I disorder.

4. A method as in claim 1 wherein the psychosis is an axis II disorder.

5. (Twice Amended) A method as in claim 1 wherein the mother and progeny have [a] compatible blood type [which is the same].

6. (Twice Amended) A method of screening for predisposition to psychosis, comprising:

(a) obtaining a sample from a maternal donor; and

(b) determining presence of an anti-Cw antibody in the sample,

wherein the presence of an anti-Cw antibody is indicative of a predisposition to [schizophrenia] psychosis if donor's progeny possess Cw antigen.

7. (Amended) A method as in Claim 6 wherein the progeny has a family history of psychosis.

8. (Amended) A method as in Claim 6 wherein the donor is pregnant.

9. A method as in Claim 8 wherein the donor is post-partum.

10. (Twice Amended) A kit for use in diagnosis of psychosis, comprising a sample containing anti-Cw, a detector that binds to anti-Cw antibody, and instructions for using the antibody and detector to diagnose a predisposition to psychosis.

11. (Twice Amended) A method for diagnosing or aiding in [the] a diagnosis of a predisposition to a psychotic disorder, comprising determining presence of anti-Cw antibody in a sample from an individual with Cw antigen, wherein the presence of anti-Cw antibody indicates a positive diagnosis.

12. (Amended) A kit for use in diagnosis of psychosis, comprising a sample containing anti-Cw antibody, a detector that binds to anti-Cw antibody; and instructions for utilization of the kit according to the method of Claim 1.

13. The method of Claim 1, further comprising utilizing a kit, comprising a sample of anti-Cw antibody, a detector that binds to anti-Cw antibody; and instructions for using the antibody and detector to diagnose a predisposition to psychosis.